REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

Claims 7-9 were pending in this application when last examined. Claims 7-9 have been examined on the merits, and stand rejected.

The present amendment amends claim 7 and adds new claims 10-12.

Claims 7-12 are now pending in this application.

Support for the recitation "20 to 60% by weight of water" in claim 7 can be found in the Specification, for example, at page 9, lines 2-6.

Support for new claims 10-12 can be found in original claims 2 and 3.

Therefore, no new matter has been added by this amendment.

II. REJECTIONS UNDER 35 U.S.C. § 103

A. US '363 in view US '874

Claims 7-9 are rejected under 35 U.S.C. § 103(a), as allegedly obvious over Mantelle et al., U.S. Patent No. 6,562,363 (US '363) in view of Oda et al., U.S. Patent No. 5,725,874 (US '874). See item 4 on pages 3-5.

This ground of rejection is respectfully traversed as applied to the amended and new claims in view of the following remarks.

The amended claims call for an external skin patch which comprises, among other ingredients, ***20 to 60% by weight of water based upon the total weight of the adhesive gel base***. US '363 and US '874 fail to render obvious the claimed invention, because they fail to teach and/or suggest this claimed element.

In fact, US '363 teaches away from a pharmaceutical composition containing water. Specifically, at column 7, lines 35-44, US '363 teaches that

> An important characteristic of the embodiments of the present invention relates to the ***substantially water-free*** and ***water-insoluble nature*** of the composition. By the term "substantially water-free" is meant that the composition contains less than about 10% by weight water, and preferably less than 5%, and most preferably less than 3% prior to its topical application. In general, it is ***desirable to avoid the addition of water entirely*** and ***to eliminate, as far as possible, the presence of water*** in the other ingredients of the composition. [Emphasis added]

Based on this disclosure, the pharmaceutical formulation of the composition of US '363 is a water-free film. Accordingly, US '363 teaches away from the inclusion of water in the composition.

In addition, US '363 teaches that "this invention relates to compositions capable of being used in wet or moist environments, especially on mucous membranes, for a prolonged period of time." See column 1, lines 13-16. Based on this teaching, the composition of US '363 is intended to be mainly applied to mucous membranes as opposed to the skin, like the present invention.

Therefore, the composition of US '363 clearly differs from the base composition of the external skin patch of the present invention which is an adhesive gel base containing ***20 to 60% by weight of water as an essential component***. US '363 teaches nothing about a skin patch having a layer containing an adhesive gel base comprising 20% by weight or more of water.

Furthermore, since US '363 ***teaches away*** from the inclusion of water, the references cannot be combined to arrive at the claimed invention.

It is well established that the prior art must contain a suggestion to combine/modify the reference teachings to arrive at the claimed invention. However, the prior art must be considered in its entirety, and references cannot be combined where the references teach away from their combination. Thus, the references cannot be combined to arrive at the claimed invention.

Also, although US'363 discloses the use of cross-linking agents, it does not teach the specifically recited aluminum compounds as the cross-linking agent. Instead, the rejection relies

on US '874 as teaching such compounds. However, US '874 teaches nothing about a composition comprising a polyvinylpyrrolidone polymer as described in US '363. Thus, there is no motivation to apply the combination of drugs described in US '363 to the preparations disclosed in US '874 to arrive at the claimed invention of an external skin patch which comprises, among other ingredients, ***20 to 60% by weight of water based upon the total weight of the adhesive gel base*** with an expectation of achieving a superior pain relief effect.

Furthermore, notwithstanding that claimed invention is not obvious over the cited prior references, it would have been difficult for one of ordinary skill in the art to discern from the teachings of US '363 and US '874 that an external skin patch of the present invention having a drug reservoir layer which comprises an adhesive gel base containing 20-60% by weight of water and medicinal components containing a specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent can achieve a superior pain relief effect. Please see the discussion below regarding the attached Declaration under 37 C.F.R. § 1.132 by Keiji Nozaki ("Nozaki Declaration") demonstrating that the claimed invention possesses an ***unexpected synergistic effect*** in comparison to administration of a random combination of anesthetic or analgesic taught in the prior art. Such unexpected synergistic effects are indicative of non-obviousness.

In view of the above, the rejection of claims 7-9 under 35 U.S.C. § 103(a) is untenable and should be withdrawn.

B. US '112 in view US '874

Claims 7-9 are rejected under 35 U.S.C. § 103(a), as allegedly obvious over Liedtke, U.S. Patent No. 5,686,112 (US '112) in view of US '874. See item 5 on pages 5-6.

This ground of rejection is respectfully traversed as applied to the amended and new claims in view of the following remarks.

The amended claims call for an external skin patch comprising a specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent, and other ingredients including 20 to 60% by weight of water based upon the total weight of the adhesive gel base. US '112 and US '874 fail to render obvious the claimed invention, because they fail to teach and/or suggest these claimed elements.

The rejection indicates that US '112 suggests a combination of non-steroidal anti-inflammatory analgesics and local anesthetics which are delivered in single dosage topical pharmaceutical form. However, US '112 does not disclose the specific combination of the nonsteroidal antiphlogistic analgesics and local anesthetics of the present invention. Instead, the active compounds described in US '112 are "analgesics and local anesthetics such as buprenorphine, fentanyl, penzocaine, morphine and morphine derivatives, lidocaine, prilocaine, mepivacaine or non-steroidal anti-rheumatics/anti-inflammatories such as indomethacin, diclofenac or etofenamate." See column 3, lines 1-9, and Claims 9-12 in column 6, lines 16-28.

Although analgesics, local anesthetics and non-steroidal anti-rheumatics/anti-inflammatories are described in column 3, lines 1-9 of US '112, the patent does not disclose special combinations of them.

Claim 9 of US '112 indicates that "said active compound is selected from the group consisting of analgesics, local anesthetics and mixtures thereof." However, the analgesics described here do not appear to include non-steroidal anti-inflammatories, because the non-steroidal anti-inflammatories are mentioned in another claim (i.e., claim 11). Also, the examples of analgesics and local anesthetics described in claim 10 do not include the examples of the non-steroidal anti-inflammatories as described in claim 12. In addition, US '112 describes in example only a combination of the oestrogen 17 β-estradiol and the gestagen norethisterone acetate which are both female hormones. See column 4, lines 43-46.

Accordingly, US '112 does not disclose the specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent of the claimed invention as acknowledged by the Examiner in lines 16-17 in item 5 on page 5 of the Office Action.

The Examiner appears to rely on the position that it is *prima facie* obvious to combine two compositions each of which is known to be useful for the same purpose, such as analgesics and anesthetics, both for relief of pain.

However, even if arbitrarily selecting any two compositions each of which is useful for relief of pain, the remarkable effect of the present invention cannot be expected.

Applicants intend to establish the nonobviousness and patentability of the claimed invention by demonstrating that the claimed invention possesses an ***unexpected synergistic effect*** in comparison to administration of a random combination of anesthetic or analgesic taught in the prior art.

The instant specification contains Examples 1-6, Comparative Examples 1-4 and a Test Example.

Also, attached herewith is a Declaration under 37 C.F.R. § 1.132 by Keiji Nozaki ("Nozaki Declaration") discussing supplemental Comparative Examples 5-8 and a Test Example 2. The Nozaki Declaration demonstrates that the claimed invention possesses an unexpected synergistic effect in comparison to administration of a random combination of anesthetic or analgesic taught in the prior art.

As evident from Comparative Examples 7-8, the combination of a local anesthetic and other analgesics such as aspirin or steroidal anti-inflammatory analgesic agents cannot achieve an unexpectedly superior pain relief effect. Also, as shown in Examples 1 and Comparative Examples 5 to 8, the amelioration ratio (effective or higher) of the external skin patches after 1 week was respectively 100% (10/10), 70% (7/10), 60% (6/10), 50% (5/10), and 60% (6/10), and the ratio of the Complete Remission was respectively 70% (7/10), 20% (2/10), 10% (1/10), 10% (1/10), and 10% (1/10).

This demonstrates that the external skin patch using the combination of the particular local anesthetic and the nonsteroidal antiphlogistic analgesic agent of the present invention (Example 1) achieves an ***unexpectedly superior pain relief effect*** compared to the external skin patches using any other combination of the compounds which are known to be useful for relief pain. See also, Comparative Examples 5-8. Thus, the Nozaki Declaration is proof that combinations other than the local anesthetic and the nonsteroidal antiphlogistic analgesic agent of the present invention cannot achieve a remarkable pain relief effect. Such unexpected synergistic effects are indicative of non-obviousness.

Furthermore, US '112 describes a pharmaceutical formulation only in a semi-solid phase, specifically in cream, emulsion, gel, suspension or ointment form and topical individual doses of the pharmaceutical formulation are situated by individual containers of a molded body.

This contrasts with the pharmaceutical formulation of the present invention which is an external skin patch comprising a substrate and a drug reservoir layer of an adhesive gel base comprising a water soluble polymeric material, a crosslinking agent selected from the group consisting of aluminum compounds, water and a humectant selected from the group consisting of polyhydric alcohols, saccharides and superabsorbent resins.

US '112 simply discloses nothing about such external skin patch of the present invention as a pharmaceutical formulation. In fact, the technical background of US '112 is entirely different from the present invention.

Furthermore, the rejection indicates that US '874 discloses a percutaneous preparation comprising a water soluble polymer, humectants such as polyhydric alcohol, water and a crosslinking agent such as aluminum compounds. US '874 also teaches that the examples of a drug comprising the preparation include some non-steroidal ant-inflammatory analgesic agents and local anesthetics. However, as discussed earlier, US '874 fails to teach the ***specific combination*** of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent of the present invention.

Moreover, the cited patents lack a motivation/suggestion to combine/modify the prior art teachings to arrive at the claimed invention.. US '874 fails to teach anything about the pharmaceutical formulation as described in US '112. Likewise, US '112 does not teach anything about such preparations as described in US '874. Accordingly, there is no motivation to apply the drug of US '112 to the preparation of US '874, or to apply the preparation of US '874 to the pharmaceutical formulation of US '112.

Thus, US '112 and US '874 fail to teach or suggest that the specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent of the present invention can achieve a superior pain relief effect. These patents also fail to contain the requisite motivation/suggestion to combine their teachings to arrive at the claimed invention.

In view of the above, the rejection of claims 7-9 under 35 U.S.C. § 103(a) is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is now in condition for allowance and early notice to that effect is hereby requested.

If it is determined that the application is not in condition for allowance, the Examiner is invited to telephone the undersigned attorney at the number below if he has any suggestions to expedite allowance of the present application.

Respectfully submitted,

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ATTACHMENT TO AMENDMENT AND REPLY:

1. Declaration under 37 C.F.R. § 1.132 by Keiji Nozaki

Sir:

I, Keiji NOZAKI, declare as follows:

I. IDENTIFICATION OF DECLARANT

I am employed by TEIKOKU SEIYAKU CO., LTD and hold the position of associate manager of New Product Planning Department.

My educational background is the following:

Graduated from Kyushu University

Bachelor's Degree in Engineering

II. DETAILS OF EXPERIMENTS

I have conducted personally or under my direction and control the following experiments:

Comparative Example 5

An external skin patch was prepared in the same production process employed in Example 1 except that 0.5 parts by weight of indomethacin was used instead of lidocaine. The total amount of the drug-containing base was fixed to 100 parts by weight by adjusting the amount of purified water. The amount of indomethacin was determined according to the amount used generally in Japan as an effective amount of the medicine.

Comparative Example 6

An external skin patch was prepared in the same production process employed in Example 1 except that 5 parts by weight of xylocaine was used instead of sodium diclofenac. The total amount of the drug-containing base was fixed to 100 parts by weight by adjusting the amount of purified water. The amount of xylocaine was determined according to the amount used generally in Japan as an effective amount of the medicine.

Comparative Example 7

An external skin patch was prepared in the same production process employed in Example 1 except that 0.1 parts by weight of betamethasone valerate which was one of the steroidal ant-inflammatory agents cited

in US 5,725,874, column 2, line 58-59 was used instead of lidocaine. The total amount of the drug-containing base was fixed to 100 parts by weight by adjusting the amount of purified water. The amount of betamethasone valerate was determined according to the amount used generally in Japan as an effective amount of the medicine.

Comparative Example 8

An external skin patch was prepared in the same production process employed in Example 1 except that 5.0 parts by weight of aspirin which was one of the general analgesic agents cited in US 5,725,874, column 3, line 13 was used instead of lidocaine. The total amount of the drug-containing base was fixed to 100 parts by weight by adjusting the amount of purified water. Since aspirin is rarely used as a drug for an external preparation, the amount of aspirin in this comparative example was determined in consideration of the circumstance of drug preparation.

Test Example 2

The external skin patches obtained in Example 1 and Comparative Examples 5 to 8 were administered randomly to 10 volunteers a group (total 50 persons) each having low back pain (i.e. plastered on the affected part) and an organoleptic examination was carried out. The duration of the administration was 12 hours a day and the test was carried out for 7 days. After the test, volunteers rated the results on a 1-to-4 scale ("complete remission", "effective", "unchanged" and "aggravation".) The results are given in Table 8.

Table 8

	Example 1	Comparative Example 5	Comparative Example 6	Comparative Example 7	Comparative Example 8
Complete Remission	7	2	1	1	1
Effective	3	5	5	4	5
Unchanged	0	2	4	5	4
Aggravation	0	1	0	0	0

As shown above, the amelioration ratio (effective or higher) of the external skin patches of Examples 1 and Comparative Examples 5 to 7 after 1 week was respectively 100% (10/10), 70% (7/10), 60% (6/10), 50% (5/10), and 60% (6/10), and the ratio of the Complete Remission was respectively 70% (7/10), 20% (2/10), 10% (1/10), 10% (1/10), and 10% (1/10).

This shows that the external skin patch using the combination of the particular local anesthetic and the nonsteroidal antiphlogistic analgesic agent of the present invention (Example 1) achieves superior pain relief effect compared to the external skin patches using any other combination of the compounds which are known to be useful for relief pain (Comparative Examples 5 - 8).

Thus, it is not obvious to the skilled artisan that using the specific combination of the local anesthetic and the nonsteroidal antiphlogistic analgesic agent of the present invention can only achieve a remarkable effect and any other random combination of drugs can not be achieved the same.

III. CONCLUSION

The foregoing experiments demonstrate that the external skin patch according to the claimed invention using a combination of local anesthetic and a non-steroidal antiphlogistic analgesic agent achieves an unexpectedly superior pain relief effect compared to an external skin patch according to the prior art using any other combination of compounds known to be effective for pain relief.

IV. VERIFICATION CLAUSE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 15/4/2004 Signature: Keiji Nozaki